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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/988,117	11/16/2001	Thomas L. Benjamin	00742/066002	8050

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EXAMINER	
LI, QIAN J	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/988,117	BENJAMIN ET AL.
	Examiner	Art Unit
	Q. Janice Li	1632

-- The MAILING DATE of this communication appears on the cover she t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-9 and 11-16* is/are rejected.

7)☒ Claim(s) *10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment, response, and Declaration of Dr. Thomas Benjamin under 37 CFR § 1.132 filed July 28, 2003 have been entered. Claim 3 has been canceled, claims 1, 2, 4, 6, 7 have been amended, and claims 11-16 are newly added. Claims 1, 2, 4-16 are pending in the application and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims, the response and Declaration will not be reiterated. The arguments in the response would be addressed to the extent that they apply to current rejection.

Information Disclosure Statement

The IDS submitted on 815/03 has been considered, however, the co-pending applications listed are not suitable to be included in the PTO-1449, therefore, have been deleted.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

WRITTEN DESCRIPTION & ENABLEMENT REQUIREMENT

Claims 1, 2, 5-9, 11-15 stand rejected or newly rejected under 35 U.S.C. 112, first paragraph, for reasons of record and following.

In the 7/28/03 response, Applicants indicated that claims 1 and 6 as amended now recite contacting abnormally proliferating cell with a Sal2 nucleic sequence having at least 90% identity to SEQ ID Nos: 2 or 4 and encodes a Sal2 protein having tumor suppressive or anti-viral activity, thus, these claims now have clear structural and functional limitations. Further, applicants argue that the specification meets the written description requirement by providing the recitation of structural features common to members of the genus of Sal2 nucleic acid sequences, and the specification provides two mutations of Sal2 protein, i.e. S73C and G744R mutation, illustrative to a broader method; and the invention intended to include any alteration in the Sal2 nucleic acid which would result in reduction of Sal2 protein.

The arguments have been fully considered but they are not persuasive for reasons of record and following.

The genus discussed in the previous Office action is drawn to *nucleic acid sequences* encoding a Sal2 polypeptide or derivatives *having tumor suppressive activity*. The structural limitation for the genus in the amended claims is that the sequences would be at least 90% identical to a nucleic acid sequence provided in SEQ ID No: 2 or 4. However, as indicated previously, a single point mutation such as S73C has made the normal Sal2 lost the tumor suppressive property, and yet the resulting mutant sequence still shares 99% sequence homology with SEQ ID No: 1, whereas the mouse Sal2 shares less than 90% sequence identity with human Sal2, yet functionally

equivalent. From these disclosures, one cannot predictably extrapolate from the teaching of the specification to determine which derivative of Sal2 polypeptide would have tumor suppressor effect. This is because according to the common knowledge in the art, each position in a peptide is uniquely defined; the number of possible peptide derivatives is very large, even for a relatively short peptide. When the number of amino acid units in the peptide chain equals *n*, the number of possible peptides is 20^n. Sal2 has more than 1000 amino acid units in the peptide chain, the possible mutation would equals to $>20^{1000}$. Therefore, lacking the disclosure of a consensus structure, the two disclosed mutations, S73C or G744R, are not the representative species of the genus. For the same reason, the skilled artisan could not envision the detailed structure of nucleic acids encompassed by claim recitation, "a proliferative disease-associated alteration in a Sal2 nucleic acid sequence". Also for the same reason, claim 9 is rejected because the specification only discloses a S73C mutant in the *human* Sal2, and fails to teach the structural homologies of Sal2 for any other species compared to hSal2, and whether such mutation in human would apply to mouse and other species is highly unpredictable.

An adequate written description for a *functional* protein requires more than a mere statement that it is part of the invention. It is not sufficient to define the sequences solely by its principal biological property, i.e. "having tumor suppressive activity" or "associated with a proliferative disease", because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any sequence with that biological property. Also, naming a type of material generically known to exist, in the

absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming all fragments that achieve a result without defining what means will do is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). With respect to the method claims, adequate description of the methods first requires an adequate description of the materials, i.e. specific chemical and physical properties of a chemical, or the sequences of a protein and nucleic acids, which provide the means for practicing the invention. The court has made it very clear "CONCEPTION OF CHEMICAL COMPOUND REQUIRES THAT INVENTOR BE ABLE TO DEFINE COMPOUND SO AS TO DISTINGUISH IT FROM OTHER MATERIALS, AND TO DESCRIBE HOW TO OBTAIN IT, RATHER THAN SIMPLY DEFINING IT SOLELY BY ITS PRINCIPAL BIOLOGICAL ACTIVITY". *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

For reasons of record and set forth above, the specification fails to meet the provision under 35 U.S.C. §112, first paragraph commensurate with the scope of the claims.

Claims 1, 2, 4-8, 11-16 stand rejected or newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for decreasing proliferation of an abnormally proliferating cell having decreased Sal2 protein levels or altered Sal2 molecular weight by contacting the cells with a plasmid encoding the wild-type Sal2 *in vitro*, does not reasonably provide enablement for doing so *in vivo* by any

route of administration with any vector. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

In the 8/27/03 response, Applicants pointed to the prophetic teaching of the specification, and submitted three new references (Exhibits 8-10) as the enablement support along with the argument to the cited art of record.

The arguments and exhibits have been fully considered but they are not persuasive for reasons of record and following.

The newly submitted references are drawn to using tumor suppressor p53 for treating tumors, while tumor suppressors such as p53 and p16 have been demonstrated to be useful by intratumoral injection of adenoviral vectors encoding such, there is no demonstrated correlation between the activity of the applicant's tumor suppressor and p53 or p16. Therefore, these references could not be used as the sole support for the *in vivo* aspect of the claimed invention.

With respect to the routes and type of nucleic acids for delivery of Sal2. First, it is noted that localized delivery, i.e. direct intratumor injection or CT-guided percutaneous fine-needle injection were used in each and every publication of exhibit 8 through 10, which illustrated the state of the art for the route of delivery at the time of the instant effective filing date. Second, it is also noted that an adenoviral vector was used in each and every publication of exhibit 8 through 10, which illustrated the state of the art for the carrier efficiency in gene therapy at the time of the instant effective filing date.

Therefore, the newly submitted references along with the previously cited teaching of *Verma et al* (Nat. 1997 Sep; 389:239-242), *Eck et al* (Phar Basis Ther 1995; 77-101), *Miller* (1995, FASEB J., Vol. 9, pages 190-199), *Deonarain* (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69), and *Zinkle et al* (Gene Ther Mol Biol 2001 Jan;6:1-24) properly support the basis of this rejection, i.e. appropriate vector and route of delivery is required for achieving a beneficial effect of gene therapy, if a systemic delivery is involved, then a vector targeting mechanism is necessary. Applicants argue that Deonarain reference does not support the rejection because the claims require neither "stable" nor "long term" transgene expression. The argument is not persuasive, because the essence of the *Deonarain* teaching cited is drawn to the necessity of *gene targeting* mechanism when a systemic route is used for vector delivery, and the necessity of transfecting a significant amount of target cells in the target organ for a therapeutic effect, which could not be achieved without a vector targeting mechanism such as ligand-receptor targeting, when the site of delivery is remote.

For reasons of record and set forth above, the specification fails to meet the provision under 35 U.S.C. §112, first paragraph commensurate with the scope of the claims.

Claim Objections

Claim 10 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 9:30 am - 6 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Q. Janice Li
Patent Examiner
Art Unit 1632

October 14, 2003

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER